Direct reprogramming of human fibroblasts toward a cardiomyocyte-like state.

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Public Summary:
We previously showed that three genes that normally guide embryonic development (abbreviated GMT) can directly reprogram cardiac fibroblasts, which are structural cells in the heart, into beating heart muscle-like cells called induced cardiomyocytes (iCMs) in vitro and in vivo. We found that, in addition to GMT, two additional genes, ESRRG and MESP1, were required to directly reprogram human fibroblasts into iCMs in vitro, and an additional two genes, MYOCD and ZFPM2, further improved reprogramming. Similar to mouse GMT-reprogrammed in vitro iCMs, human iCM reprogramming was stable and displayed comparable quality of reprogramming.

Scientific Abstract:
Direct reprogramming of adult somatic cells into alternative cell types has been shown for several lineages. We previously showed that GATA4, MEF2C, and TBX5 (GMT) directly reprogrammed nonmyocyte mouse heart cells into induced cardiomyocyte-like cells (iCMs) in vitro and in vivo. However, GMT alone appears insufficient in human fibroblasts, at least in vitro. Here, we show that GMT plus ESRRG and MESP1 induced global cardiac gene-expression and phenotypic shifts in human fibroblasts derived from embryonic stem cells, fetal heart, and neonatal skin. Adding Myocardin and ZFPM2 enhanced reprogramming, including sarcomere formation, calcium transients, and action potentials, although the efficiency remained low. Human iCM reprogramming was epigenetically stable. Furthermore, we found that transforming growth factor beta signaling was important for, and improved the efficiency of, human iCM reprogramming. These findings demonstrate that human fibroblasts can be directly reprogrammed toward the cardiac lineage, and lay the foundation for future refinements in vitro and in vivo.